Clinical Aspects and Regulatory Requirements for Nanomedicines

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18.1 INTRODUCTION

18.1.1 Opportunities and Challenges of Nanotechnology

Nanotechnology involves utilizing scientific knowledge to tune materials at nanoscale. The most significant advantage of the nanomedicines is their unique characteristics and phenomena exhibited by a smaller size (1–100 nm). Using nanoscale size range, many researchers developed targeted nanoparticles that have specificity towards a particular cell or tissue thus improving the efficacy and reducing the side effects (Sharma et al., 2018).

Recently, by nanotechnology one can further make advances in the instruments and medical devices used in surgical procedures thereby reducing the invasiveness, risk associated with postoperative infections, and thus overall shortening the recovery time. Thus nanotechnology also contributes to improving the life quality, extension of life expectancy, and thus making the cost affordable and effective (Kumar et al., 2018).

Nanotechnology-based research originates from the development of targeted delivery systems like liposomes and dendrimers to diagnostic nanoparticles like carbon nanotubes. However, researchers need to address the fate and transport of such nanoparticles in biological systems. Safety and risks associated with the use of these nanoparticles should be clearly described and supported by evidence (Sanvicens and Marco, 2008).

Regulatory agencies, public groups, and insurance agencies should work altogether for proper implementation of nanomedicines. This will also ensure that challenges are met at an early stage. A public health professional can enhance the development of nanomedicine by collecting and analyzing epidemiologic data to conclude the effectiveness of nanodrugs or nanoparticles based delivery strategy. They can also support by promoting to get more funds for research (Pautler and Brenner, 2010).

18.1.2 Nanomedicines: A Short Overview

Nanomedicines are purposefully designed systems for specific clinical application in nanoscale range with tunable specific properties enhancing the targeting or biodistribution profile of the drug. Nanomedicines involve molecules with diverse structures, namely liposomes, polymeric nanoparticles, carbon nanotubes, quantum dots, gold nanoparticles, magnetic nanoparticles, dendrimers, polymeric micelles, and viral vectors (Tekade et al., 2017b). These nanomedicines either encapsulate or solubilize the drug to improve its solubility or stability or provide us with magnetic, thermal diagnostic, or imaging agents.

Several nanomedicines have reached the market especially in the area of oncology and are proven to be more efficient over the existing ones. They are emerging as multifunctional nanocarriers owing to the following properties. They can identify malignant cells over normal cells via targeting and hence reduce the off-target side effects and reduce the dose and dosing frequency. Real-time monitoring of drug release and temporal control of drug release is possible. Their optical properties help to visualize their location in the body when administered by a predetermined route. Also, codeelivery of a drug is possible with these nanocarriers depicting synergism (Choudhury et al., 2017).

Liposomes are spherical structures composed of one or more concentric lipid bilayers with an aqueous core. Cationic liposomes have shown enhanced drug delivery due to its...
18.1 INTRODUCTION

Charge. Further, they are Pegylated to increase blood circulation time and avoid RES uptake (Honda et al., 2013). Polymeric micelles are composed of an amphiphilic block copolymer containing hydrophilic and hydrophobic moiety. They have a larger size, better stability, and are uptaken by endosomal mechanism thus preventing efflux of entrapped drug (Kwon and Okano, 1996). Polymeric nanoparticles are composed of polymers like hyaluronic acid, albumin, and their size depends upon the method used for preparation. They can be surface modified and tagged with ligand-targeting to particular cancerous cells (Kesharwani et al., 2016). Controlled release or sustained release of drug can be obtained. The drug can be either physically entrapped or conjugated to the surface of polymeric nanoparticles (Tekade et al., 2015).

Carbon nanotubes have unique physical architecture, a large surface area with ease of scale-up, and high drug loading, making them versatile nanocarriers (Kuche et al., 2018). Quantum dots are semiconductor nanoparticles made up of material such as silicon, cadmium selenide, cadmium sulfide, or indium arsenide that glow a particular color after being illuminated by light.

They possess good chemical and photostability, high quantum yield, and size tunable light emission. Thus they have wide application in the fields of sensors, drug delivery, and biomedical imaging (Probst et al., 2013). Dendrimers are monodisperse, highly branched polymers with easily modifiable surfaces. They can increase the solubility of the hydrophobic drug and also load a hydrophilic drug. Many surface modifications of dendrimers have been made for targeting them towards cancer therapy (Tekade et al., 2008). Nanotherapy is an emerging therapy due to its various advantages over conventional therapeutics.

18.1.3 Next Generation Nanomedicines and Nanosimilars

Nanomedicine’s advancement has led to the development of combination nanomedicines, imaging agents, and diagnostic agents. Advancement in technology has paved the way for further enhancing nanomedicines. Currently, nanomedicines are emerging as a platform for delivery of siRNA or miRNA (Tambe et al., 2017).

These RNAi are unstable and degraded by the RNase found in physiological fluids. Thus nanocarriers encapsulate such RNAi protecting them for the RNase degradation and improving their targeting specificity and stability. Exosomes, fusion proteins, and RNAi nanoparticles are the latest advancements in nanotherapy. Nanosimilars are a follow-up to the product of a reference nanomedicine (Maheshwari et al., 2017).

18.1.4 Nanomedicines in the Market

Despite various difficulties along the development process and a lot of competition from the conventional medicines still, some nanomedicines have been approved by FDA, EMA, or foreign regulatory agencies (Tekade et al., 2017a). Nearly 40% of these are protein—polymer conjugates and liposomes. Mainly nanomedicines are mostly developed for targeted therapy for cancer. Nanomedicines are conjugated with ligand rendering them
specificity towards cancer cells and thus protecting the normal cells and reducing off-target side effects.

Nanomedicines have difficulty in entering the market due to the higher costs involved in clinical development and their regulatory approval, which are not compensated due to limited sales of nanomedicines (Wang et al., 2015). Doxil is the first approved nanomedicine containing doxorubicin loaded PEGylated liposomes for the treatment of cancers such as ovarian cancer, metastatic breast cancer, Kaposi sarcoma in HIV patients, and multiple myeloma. However to date still many challenges in the development of these nanomedicines are to be met (Jiang et al., 2007).

18.2 REGULATORY PERSPECTIVE

18.2.1 Development of Nanomedicines

There are large numbers of nanomedicines existing in the market. However, the lack of specific general protocol for study the safety or efficacy of these nanomedicines is hampering their development. General methods described for testing the safety, toxicity, compatibility, or efficacy of conventional dosage forms are only employed for the testing of nanomedicines. From the regulatory perspective, the API of nanomedicines dictates the specifications be analyzed within the regulatory context. Proteins or antibodies as biological entities used in nanomedicines, and then the innovative product, must follow the regulations defined for new chemical entities and biological medicinal plants (Sainz et al., 2015).

Nanomedicines' clinical utility is strongly dependent on their physicochemical properties and surface modifications. These properties are modified during the manufacturing or developmental stages of nanomedicines. To date, only methods that evaluate the physicochemical characteristics of these nanomedicines are available (Min et al., 2015). However, it is still required to develop a quality control assay that will evaluate the effect of these physicochemical modifications on the performance of nanomedicines like therapeutic efficacy and biological properties. Thus researchers need to develop methods that not only measure physicochemical properties of nanomedicines like size, charge, and size variability but also can determine the performance of nanomedicines like drug release, protein binding, and specific cellular uptake (Muthu et al., 2014).

Nanomedicines are absorbed by immune cells, thus determining their immunotoxicity during preclinical studies is an essential step in the development of nanomedicines. Also some nanomedicines like dendrimers and carbon nanotubes possess toxicity that needs to be overcome by further surface modifications. Another hurdle is the large-scale manufacturing of these nanomedicines, which is difficult due to process variation and lack of scalability (Desai, 2012).

Therefore one needs to determine the critical process parameters and control them to achieve production of these nanomedicines at large scale. Nowadays quality by design approaches utilizing PAT (process analytical technologies) has allowed for online or line detection. International Conference on Harmonization (ICH) Guidelines Q8, Q9, and Q10 describe novel pharmaceutical development regulations, which can further help to control
the nanomedicines. Regulators from the United States, Europe, and Japan are putting in effort to develop such nanomedicine regulatory approaches through the ICH. Therefore many such harmonized assays are needed to clearly determine in vivo safety and efficacy of these nanomedicines (Tinkle et al., 2014).

Detection of low levels of these nanocarriers that differentiates them from their aggregate form or metabolized form is needed. Thus techniques like fluorescence imaging or cellular imaging have been developed to overcome this limitation. The data that should be provided before and during the product lifecycle of nanomedicines for marketing approval requires animal and clinical studies, creating another hurdle in the development of nanomedicines (Gaspar, 2007). The regulatory system in Europe allows the marketing authorization applicants to receive scientific counseling from the regulators during early stages of R&D.

This provides a harmonized environment wherein if nanomedicines are found to be more toxic or less efficacious then they can be modified or tuned accordingly to achieve lesser toxicity and better therapeutic efficacy. Nowadays additionally the socioeconomic potential of these nanomedicines can also be determined to evaluate the social and economic benefits compared with those of the existing treatments (Gaspar and Duncan, 2009).

### 18.2.2 Next Generation Nanomedicines

Next generation nanomedicines demand more evidence of enhanced clinical efficacy compared with existing ones, and also emphasize more on pharmacoeconomic evaluation. Also, development in biopharmaceuticals has further led to the formation of next generation nanomedicines.

Nowadays, nanosimilars are being focused on by the regulatory agencies. These tend to combine a generic drug and nanocarriers as innovative recipients. Additionally, debate over similar formulations within nonbiological complex drugs (NBCDs) has illuminated a number of major critical issues in specific formulations like iron oxide nanoparticles, liposomes, and polymeric micelles. Thus they are under increased regulatory scrutiny (Ehmann and Pita, 2016).

Various regulatory agencies like EMEA, FDA, and agencies from Japan and other countries like Switzerland and Canada started their discussion on the classification of nanomaterial and how to regulate them to ensure proper efficacy and safety of these materials. The major outputs from this burst of new regulatory initiatives include a set of guidance documents from the EMA related to iron-oxide nanoparticles, similar liposomal products, and polymeric micelles. FDA also has documents on liposomal products and scientific discussion about regulatory implications on NBCDs (Wagner et al., 2006). Table 18.1 describes liposomal and nonliposomal lipid formulation approved by the regulatory agency FDA, TGA, and EMA. The first liposomal product ( Abelcet ) was approved in 1995 by FDA and TGA; from then to now, many other companies have also come up with lipid-based nanoformulations.

Thus increased concern at the United States and European levels demonstrated that harmonization is essential for the quality of nanomedicines. The Nanotechnology Characterization Laboratory at the National Cancer Institute in the US gathered all the
### TABLE 18.1 Lipid-Based Nanomedicines Approved by FDA, TGA, and EMA

<table>
<thead>
<tr>
<th>Type of Nanoformulation</th>
<th>Trade Name</th>
<th>Active Pharmaceutical Ingredients</th>
<th>Indication</th>
<th>Approval Date</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonliposomal liposome formulation</td>
<td>Abelcet</td>
<td>Amphotericin B</td>
<td>Systemic fungal infections when amphotericin B is not recommended</td>
<td>FDA (1995) &amp; TGA</td>
<td>Sigma-Tau, Cephalon, Enzon, Elan/Aukermes</td>
</tr>
<tr>
<td></td>
<td>Amphotec</td>
<td>Amphotericin B</td>
<td>Invasive aspergillosis when amphotericin B is not recommended</td>
<td>FDA (1996)</td>
<td>Akpharma, Three Rivers/Astra</td>
</tr>
<tr>
<td></td>
<td>DaunoXome</td>
<td>Daunorubicin citrate</td>
<td>HIV-related Kaposi’s sarcoma</td>
<td>FDA (1996)</td>
<td>Nexeon, Galmed Sciences, Galen, Teva</td>
</tr>
<tr>
<td></td>
<td>Calyx</td>
<td>Pegylated liposomes</td>
<td>Metastatic breast cancer, AIDS-related Kaposi’s syndrome</td>
<td>EMA &amp; TGA</td>
<td>Janssen</td>
</tr>
<tr>
<td></td>
<td>Curosurf</td>
<td>Poractant-ALFA</td>
<td>Respiratory Distress Syndrome (RDS) in premature infants</td>
<td>FDA (1999)</td>
<td>Chiesi</td>
</tr>
<tr>
<td></td>
<td>Visudyne v</td>
<td>Verteporin</td>
<td>Photodynamic therapy</td>
<td>FDA (2000) &amp; TGA</td>
<td>Valeant, QLT Ophthalmics</td>
</tr>
<tr>
<td></td>
<td>Myocet</td>
<td>Doxorubicin</td>
<td>Metastatic breast cancer</td>
<td>EMA (2000)</td>
<td>Cephalon/Zeneus, Elan, Sopherian Therapeutics</td>
</tr>
<tr>
<td></td>
<td>Definity</td>
<td>Perflutren</td>
<td>Contrast agent</td>
<td>FDA (2001)</td>
<td>Lantheus, Bristol Myers Squibb</td>
</tr>
<tr>
<td></td>
<td>DepoDur</td>
<td>Morphinesulfate</td>
<td>Chronic pain</td>
<td>FDA (2004) &amp; TGA</td>
<td>Pacira</td>
</tr>
<tr>
<td></td>
<td>Marqibo</td>
<td>Vincristine sulfate</td>
<td>Philadelphia chromosome and acute lymphoblastic leukemia</td>
<td>FDA (2012)</td>
<td>Talon Therapeutics</td>
</tr>
<tr>
<td></td>
<td>Mepact</td>
<td>Milamsartide</td>
<td>Osteosarcoma</td>
<td>EMA (2009)</td>
<td>Takeda oncology</td>
</tr>
<tr>
<td></td>
<td>Onivyde</td>
<td>Irinotecan</td>
<td>Pancreatic cancer</td>
<td>FDA (2015)</td>
<td>Ipsen Pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td>Vyxeus</td>
<td>Daunorubicin and cytarabine</td>
<td>AML, AML with myelodysplasia-related changes</td>
<td>FDA (2017)</td>
<td>Jazz Pharmaceuticals</td>
</tr>
</tbody>
</table>


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**BASIC FUNDAMENTALS OF DRUG DELIVERY**

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data on nanomedicines in oncology, thus taking one step closer to the development of next generation nanomedicines. Nowadays even integrated approaches of nanomedicines like multiplex medical devices or theragnostic nanoparticles, which can be used for both diagnosis as well as therapy, are being developed (Fan et al., 2012).

Indeed integration between material science and translational issues like validation of appropriate disease models is essential for developing regulation of nanomedicines. Nevertheless, Innovative Medicines Initiative (IMI) in Europe and the National Centre for Advancing Translational Sciences (NCTAS/NIH) in the United States are major platforms contributing to the development of personalized medicines and nanomedicines through innovative technology.

18.3 ROLE OF THE VARIOUS REGULATORY AGENCIES INVOLVED IN REGULATION OF NANOMEDICINES

18.3.1 United States Food and Drug Administration

Nanomedicines comprise of varying physicochemical properties at the nanoscale, thus not-specific regulations compliance for nanomedicines has been provided by the FDA. Therefore by enhancing the expertise in tools used for determination of safety and efficacy, FDA can bring about the development of new products and devices. FDA intends to ensure transparent and predictable regulatory pathways grounded in the best available science (Sanhai et al., 2008).

Regulatory approach of nanomedicines by FDA will have the following attributes. Firstly FDA will be maintaining product specific and science-based regulatory policy. Depending upon the effects of nanomedicines in particular biological and mechanical environments, they will be analyzed separately. Technical assessment will be product specific thus it would be beneficial for the manufacturers that they consult with the FDA during their early product development so that regulatory issues regarding nanomedicines are addressed during the early development phase itself (Harris, 2009).

Secondly, where premarket review authority exists, attention to nanomaterials is being incorporated into standing procedures. The premarket review involves submission by the applicant’s data related to safety, regulatory status, or effectiveness of nanomedicines. Individual premarket review procedures include attention to whether the use of nanomaterials suggests the need for additional data on safety or effectiveness, as applicable.

As discussed previously initial consultation with FDA in case of nanotechnology products will help the manufacturers to get advice on safety information or designing any necessary postmarketing safety oversight before the products have received marketing approval. Thirdly, FDA will continue to monitor the marketplace for nanomedicines and take any appropriate actions if required (Miller, 2003). Thus FDA is playing an important role in accumulating data, devising testing protocols, and ensuring the safety of nanomedicines. To facilitate the regulation of nanomedicines, FDA has formed an internal Nanotechnology Interest Group (“NTIG”) composed of representatives from all its regulatory centers.
The Nanotechnological Task Force additionally is formed by FDA for regulation of nanomedicines. The 2013 Nanotechnology Regulatory Science Research Plan is one program started by the FDA to address key scientific gaps in knowledge, methods, or tools needed to make regulatory assessments of nanotechnology products. It contains four areas, namely staff training and professional development, laboratory core facilities, the Collaborative Opportunities for Research Excellence in Science (CORES) Program, and FDA Coordination led by FDA Nanotechnology Task Force, with representatives from across the agency, will facilitate communication on nanotechnology regulatory science both within FDA and with national and international stakeholders, and provide overall coordination of FDA’s nanotechnology regulatory science research efforts. Thus the implementation of such a program depicts the paradigm shift towards regulation of nanotechnology products to ensure its safety to humans and the environment (Etheridge et al., 2013).

18.3.2 Therapeutic Goods Administration

The Therapeutic Goods Administration (TGA) describes nanotechnology involving a wide range of methods involved in the production and engineering of structures and systems by controlling size and shape at the nanometer scale. The National Nanotechnology Strategy (NNS) superseded by the National Enabling Technologies Strategy (NETS) aimed to allow Australia to capture the benefits of nanotechnology while addressing any safety concerns (Faunce, 2007).

Monash’s review in 2007 noted some key findings that showed Australia’s regulatory framework generally suited the regulation of nanotechnology-based products. Thus there was no major change needed in the regulatory guidelines; however some minor amendments could be done. TGA responded to the NNS report by the establishment of the TGA Nanotechnology Focus Group to review existing regulatory arrangements for therapeutics and make the changes as required to enhance the regulation of nanomedicines. Additionally, the development of the focus group builds a scientific environment within the organization and also helps in establishing international and national collaborations (Faunce, 2009a).

TGA is better regulating nanotechnological products by having a high level of expertise to evaluate new technologies. Additionally, it has the legislated authority to require additional data in support of the safety assessment of new materials and for the most part deals with applicants that have the technical expertise to adequately address key safety issues (Faunce, 2009b). Nanoformulations approved by TGA are described in Table 18.2.

TGA conducts nanotechnological training programs wherein physical or chemical properties of nanomaterials are studied versus conventional ones, and their benefits in the clinical setting are determined. It includes studying in vitro behavior of nanoparticles. Additionally, the pharmacokinetics of nanoparticles like half-life, bioavailability, etc. are also studied. Further in vitro and in vivo toxicity of nanoparticles are assessed followed by risk assessment and risk minimization. Thus TGA as a whole is on the forefront in regulating the nanomedicines (Hodge et al., 2009).
### Table 18.2 Polymeric, Nanocrystals, and Enzymes Conjugate Based Nanomedicines Approved by FDA, TGA, and EMA

<table>
<thead>
<tr>
<th>Type of Nanoformulation</th>
<th>Trade Name</th>
<th>Active Pharmaceutical Ingredients</th>
<th>Indication</th>
<th>Approval Date</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymeric nanoparticles</td>
<td>Copaxone</td>
<td>Glatiramer acetate</td>
<td>Multiple sclerosis</td>
<td>FDA (1996) &amp; TGA</td>
<td>Teva</td>
</tr>
<tr>
<td></td>
<td>Kryostexx</td>
<td>Pegloticase</td>
<td>Chronic gout</td>
<td>FDA (2010)</td>
<td>Savient Pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td>Adynovate</td>
<td>Antiinflammatory factor (recombinant)</td>
<td>Hemophilia</td>
<td>FDA (2016)</td>
<td>Shire</td>
</tr>
<tr>
<td></td>
<td>Cimzia</td>
<td>Certolizumab pegol</td>
<td>Crohn's disease, Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis</td>
<td>FDA (2018)</td>
<td>UCB</td>
</tr>
<tr>
<td></td>
<td>Mircera</td>
<td>Methoxy polyethylene glycol-epoetin beta</td>
<td>Anemia associated with chronic kidney diseases</td>
<td>FDA (2018)</td>
<td>Vifor</td>
</tr>
<tr>
<td>Nanocrystal</td>
<td>Naprelan</td>
<td>Naproxen sodium</td>
<td>Rheumatoid arthritis and osteoarthritis, gout</td>
<td>FDA (1996)</td>
<td>Almaco, Elan/Alkermes, Wyeth</td>
</tr>
<tr>
<td></td>
<td>Ritalin LA</td>
<td>Methylphenidate hydrochloride</td>
<td>Attention deficit hyperactivity disorder</td>
<td>FDA (2002)</td>
<td>Novartis</td>
</tr>
<tr>
<td></td>
<td>Zanaflex</td>
<td>Tizanidine HCl</td>
<td>Muscle relaxant</td>
<td>FDA (2002)</td>
<td>Acorda</td>
</tr>
<tr>
<td></td>
<td>Avinza</td>
<td>Morphine sulfate</td>
<td>Moderate/severe pain</td>
<td>FDA (2002)</td>
<td>Elan/Alkermes, Pfizer</td>
</tr>
<tr>
<td></td>
<td>Vitoss</td>
<td>Calcium phosphate</td>
<td>Bone substitute</td>
<td>FDA (2003)</td>
<td>Stryker</td>
</tr>
<tr>
<td></td>
<td>Triglide</td>
<td>Fenoldipine</td>
<td>Diukosipemias</td>
<td>FDA (2005)</td>
<td>Skye, First Horizon, Sciele</td>
</tr>
</tbody>
</table>

(Continued)
### TABLE 18.2 (Continued)

<table>
<thead>
<tr>
<th>Type of Nanoformulation</th>
<th>Trade Name</th>
<th>Active Pharmaceutical Ingredients</th>
<th>Indication</th>
<th>Approval Date</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focalin XR</td>
<td>Dexmethyllphenidate hydrochloride</td>
<td>Attention deficit hyperactivity disorder</td>
<td>FDA (2005)</td>
<td>Novartis/Alkermes</td>
<td></td>
</tr>
<tr>
<td>Megace ES</td>
<td>Megestrol acetate</td>
<td>Anorexia, cachexia, breast and endometrial cancer</td>
<td>FDA (2005)</td>
<td>Par</td>
<td></td>
</tr>
<tr>
<td>Zyprexa</td>
<td>Olanzapine</td>
<td>Schizophrenia</td>
<td>FDA (2009)</td>
<td>Lilly</td>
<td></td>
</tr>
<tr>
<td>Equivite Bone</td>
<td>Hydroxyapatite</td>
<td>Bone substitute</td>
<td>FDA (2009)</td>
<td>Zimmer Biometi</td>
<td></td>
</tr>
<tr>
<td>Anti-enzymes conjugate</td>
<td>Adagen EPEGylated adenovirus deaminase</td>
<td>Severe combined immunodeficiency disease</td>
<td>FDA (1990)</td>
<td>Sigma-Tau, Lintron</td>
<td></td>
</tr>
</tbody>
</table>


#### 18.3.3 European Medicine Agency

The European Medical Agency’s (EMA) scientific guidelines help the manufacturer to prepare marketing authorization applications for human medicines. Guidelines reflect a harmonized approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety, and efficacy set out in the Community directives. EMA follows a different approach to nanomedicines by collaborating with various organizations in the EU enabling a platform for both scientific and regulatory aspects. This governs at an early stage the benefit/risk model and good scientific advice at an early stage of nanomedicines development and evaluates the need for additional guidance (Hafner et al., 2014).

The framework of EMA states that they evaluate nanomedicines based on established principles of benefit/risk analysis unlikely by technology. The evaluation also includes risk management plans and environmental risk assessment. Evaluation is performed by a specialized multidisciplinary expertise group, which includes mixed personnel from industry, academia, and regulatory experts. This group was firstly created in 2009 and later reinforced in 2011. They are also involved in formulating guidelines. Further enhancement in nanomedicines is achieved by close EU cooperation with other scientific committees (e.g., SCENIHR, EFSA), networks (QNano, ETPNano), and with the European Commission.

Additionally, international cooperation was achieved as EMA chairs an international regulators expert group like US FDA, Japan MHLW, Health Canada, TGA Australia. Thus, EMA maintains an amalgam of experts from various disciplines pooling the quality, safety, and efficacy evaluation of nanomedicines (Hafner et al., 2014).

In 2011 the CHMP commissioned a multidisciplinary drafting group to develop a series of four reflection papers on current scientific and regulatory thinking for nanomedicines. These reflection papers covered the development of both nanomedicines and nanosimilars.
18.4 CLINICAL ASPECTS OF NANOMEDICINES

The four reflection papers cover data requirements for intravenous iron-based nanocolloidal products developed with reference to an innovator medicinal product, development of block-copolymer-micelle medicinal products, data requirements for intravenous liposomal products developed with reference to an innovator liposomal product and surface coating, and general issues for consideration regarding parenteral administration of coated nanomedicine products (Havel et al., 2016).

Firstly, the reflection paper on intravenous iron-based nanocolloidal products developed concerning an innovator medicinal product assisted the generation of relevant quality, nonclinical and clinical comparative data to support a marketing authorization of a nanosized colloidal intravenous iron-based preparation developed as a treatment for iron deficiency anemia concerning a nanosized colloidal innovator product. It also included changes made to the manufacturing process of the same and also iron-based nanocolloidal products administered for other diseases (Crommelin et al., 2014).

Secondly, the reflection paper on intravenous liposomal products developed concerning an innovator liposomal product assisted in the generation of relevant quality, nonclinical, and clinical data to support a marketing authorization of intravenous liposomal products developed concerning an innovator liposomal product. Additionally, the vesicular system administered other than the intravenous route was also included (Mühlbach et al., 2015).

Thirdly, the joint EMA/MHLW reflection paper on block copolymer micelle medicinal products involved pharmaceutical development, clinical, and nonclinical studies of block copolymer micelle containing medicinal products developed to modify its pharmacokinetic, stability, and distribution profile. Lastly, the reflection paper on surface coating included the factors (biodistribution, pharmacokinetics) to be considered for a covalent or noncovalent coating of nanomaterials.

Additionally, the impact of this coating on the safety and efficacy of the products is also considered. Also, the quality, clinical, and nonclinical data defining critical product characteristics of coated nanomedicines. Thus existing EMA has efficient guidelines for regulation of nanomedicines and also can address issues regarding its development ensuring the safety and efficacy of nanomedicines (Eickhoff, 2015; Bartlett et al., 2015).

Nanoformulations approved by EMA are depicted in Tables 18.1–18.3. Table 18.1 emphasizes liposomal and nonliposomal lipid formulation. Table 18.2 emphasizes polymeric, nanocrystal, and enzymes based nanoformulations. Table 18.3 emphasizes antibody, surfactant based, metal, protein—drug conjugates, aptamer, and PEGylated drugs diagnostic multiparticulate systems.

18.4 CLINICAL ASPECTS OF NANOMEDICINES

18.4.1 Preclinical

Preclinical evaluation of nanomedicines involves testing them in either animals or cells or tissues. These preliminary in vitro and in vivo tests are essential to prevent the latter failure of these nanomedicines mainly due to toxicity. Thus, various parameters are measured in an in vivo animal model like safety, pharmacology, and efficacy profile of the nanomedicines. Immunotoxicity as a part of traditional toxicity studies is also determined.
### TABLE 18.3 Antibody, Surfactant Based, Metal, Protein—Drug Conjugates, Aptamer, PEGylated and Multiparticulate Nanomedicines Approved by FDA, TGA, and EMA

<table>
<thead>
<tr>
<th>Type of Nanosystem</th>
<th>Trade Name</th>
<th>Active Pharmaceutical Ingredients</th>
<th>Indication</th>
<th>Approval Date</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cimzia</td>
<td>Certolizumab pegol</td>
<td>Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis</td>
<td>FDA (2008) &amp; TGA</td>
<td>UCB</td>
</tr>
<tr>
<td>Surfactants based</td>
<td>Pungione</td>
<td>Amphotericin B</td>
<td>Systemic fungal infections</td>
<td>FDA (1966)</td>
<td>Bristol-Myers Squibb, AstraZeneca</td>
</tr>
<tr>
<td></td>
<td>Diprivan</td>
<td>Propofol</td>
<td>Anesthetic</td>
<td>FDA (1989)</td>
<td>Fresenius Kabi, Medisic/Novavax/Erpart, Graceway</td>
</tr>
<tr>
<td></td>
<td>Estradex</td>
<td>Estradiol benzoate</td>
<td>Reduction of vasomotor symptoms during menopause</td>
<td>FDA (2003)</td>
<td></td>
</tr>
<tr>
<td>Metal</td>
<td>INFEd</td>
<td>Iron Dextran (Low MW)</td>
<td>Iron deficiency in chronic kidney disease</td>
<td>FDA (1957)</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td></td>
<td>Dexfermus</td>
<td>Iron Dextran (High MW)</td>
<td>Iron deficiency in chronic kidney disease</td>
<td>FDA (1957)</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td></td>
<td>Ferrlecit</td>
<td>Sodium ferric gluconate complex</td>
<td>Iron deficiency anemia</td>
<td>FDA (1999)</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td></td>
<td>Venofor</td>
<td>Iron succrose (iron/follodable hydroxide succrose complex)</td>
<td>Iron deficiency</td>
<td>FDA (2000) &amp; TGA</td>
<td>Lutipold, Vifor France</td>
</tr>
<tr>
<td></td>
<td>Fosrenol</td>
<td>Lanthanum carbonate</td>
<td>End-stage renal disease</td>
<td>FDA (2004)</td>
<td>Shire</td>
</tr>
<tr>
<td></td>
<td>Feraheme</td>
<td>Ferumoxytol</td>
<td>Treatment of iron deficiency anemia in patients with chronic kidney disease</td>
<td>FDA (2009)</td>
<td>AMAG</td>
</tr>
<tr>
<td>Protein—drug conjugates</td>
<td>Ontak</td>
<td>Denileukin diftitox</td>
<td>Persistent or recurrent cutaneous T-cell lymphoma</td>
<td>FDA (1999)</td>
<td>Eisai</td>
</tr>
<tr>
<td></td>
<td>Kadcyla</td>
<td>Ado-Trastuzumab Emtansine</td>
<td>Metastatic breast cancer</td>
<td>FDA (2013)</td>
<td>Genentech</td>
</tr>
<tr>
<td>PEGylated Drugs</td>
<td>Oncaspargi</td>
<td>PEGylated 1-asparaginase</td>
<td>Lymphoblastic leukemia</td>
<td>FDA (1994)</td>
<td>Enzon/Schering-Plough, Sigma-Tau</td>
</tr>
<tr>
<td></td>
<td>Peglntron</td>
<td>PEGylated interferon alfa-2b</td>
<td>Hepatitis C in patients with compensated liver disease</td>
<td>FDA (2001), EMA (2000) &amp; TGA</td>
<td>Schering-Plough, Merck</td>
</tr>
</tbody>
</table>

*Continued*
### TABLE 18.3 (Continued)

<table>
<thead>
<tr>
<th>Type of Nanoformulation</th>
<th>Trade Name</th>
<th>Active Pharmaceutical Ingredients</th>
<th>Indication</th>
<th>Approval Date</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somavert</td>
<td>Pegylated human growth hormone receptor agonist (Pegvisomant)</td>
<td>Acromegaly</td>
<td>FDA (2003), EMA (2002) &amp; TGA</td>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>Plegridy</td>
<td>Pegylated IFN beta-1a</td>
<td>Multiple sclerosis</td>
<td>FDA (2014)</td>
<td>Biogen</td>
<td></td>
</tr>
<tr>
<td>Rebinyn</td>
<td>Coagulation factor IX</td>
<td>Hemophilia B</td>
<td>FDA (2017)</td>
<td>NovoNordisk</td>
<td></td>
</tr>
<tr>
<td>Ziretta</td>
<td>Triamcinolone acetonide</td>
<td>Osteoarthritis knee pain</td>
<td>FDA (2017)</td>
<td>Flexion Therapeutics</td>
<td></td>
</tr>
<tr>
<td>Diagnostic</td>
<td>Sinerem</td>
<td>Diagnostic agent superparamagnetic iron oxide coated nanoparticles</td>
<td>In vivo characterization of lymph nodes</td>
<td>EMA</td>
<td>Guerbet</td>
</tr>
</tbody>
</table>

Multiparticulate system

| Verelan                  | Versapamild | Hypertension                  | FDA (1998)                | Elan/Alkermes |
| Verelan                  | Versapamild | Hypertension                  | FDA (1998)                | Elan/Alkermes |

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(Caster et al., 2017). As many products approved by FDA were found to be withdrawn due to immunotoxicity after entering the market. Also, initial preclinical testing provides evidence to reject lead molecules depicting either immunotoxicity or toxicity or any other characteristics unfavorable for good drug candidates and also provides a platform to reduce, replace, and refine the use of laboratory animals. In vitro assays involve LAL assay for determination of immunotoxicity and MTT assay (Tekade et al., 2009). In vivo studies involve acute toxicity, acute systemic toxicity, and long-term toxicity studies carried out as per OECD guidelines. Due to the smaller size of nanomaterials determining environmental toxicity is also of utmost importance.

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18.4.2 Clinical

Before initiating clinical trials, the investigators need to submit to the FDA data regarding the preclinical studies involving either animals or cells or tissues or in vitro. Then after getting approval Phase, 1 clinical trials of nanomedicines are conducted in small subjects (25–100) involve assessment of safety, tolerability, and pharmacokinetic properties. It also includes determination of maximum tolerated dose. After the nanomedicines are found to be safe in phase I study, further phase II clinical trials are conducted in more subjects (100–500) (Libutti et al., 2010).

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BASIC FUNDAMENTALS OF DRUG DELIVERY
Phase II clinical trials include exploratory studies in disease subjects to determine the efficacy of the nanomedicines. Additionally, dose range is also determined. After successful completion of phase II clinical trials, phase III studies are conducted in patients (500–3000) most likely to receive the treatment postapproval for confirmation of safety and efficacy of nanomedicines. After the phase III clinical trials, successful completion renders the nanomedicines approved for marketing. Phase IV clinical trials are conducted further to gather knowledge regarding the side effects, adverse reactions, safety, and tolerability when the nanomedicines enter the market (Wang et al., 2013).

If the clinical study involves an investigational drug, biologics, or medical device, then its study must be approved by an institutional review board (IRB). Briefly, it should consider that risks will be minimum, risk to benefit ratio should be optimum, informed consent is properly sought and documented, selection of subjects will be equitable, vulnerable populations will be protected, provisions for data and safety monitoring are made, and confidentiality and privacy of the data are maintained (Fatehi et al., 2012).

18.4.3 Ethical Issues in Clinical Trials Involving Nanomedicines

Nanomedicines being tested in clinical trials are of two types firstly drug delivery devices or diagnostic devices. Gold nanoparticles are used to detect proteins and DNA present in a biological sample on the contrary quantum dots due to their size-dependent fluorescence activity to illuminate organs like such as tumors or lymph nodes. However, in case of gold nanoparticles there is minimal risk to humans as tissues samples are required for the diagnosis whereas in the case of quantum dots they need to be administered in the body and can thereby damage healthy cells as they contain heavy metals that tend to diffuse in the nearby cells and disrupt the cellular functions. Although quantum dots can be a substitute for radioactive dyes, they are still not used due to this risk (Resnik and Tinkle, 2007a).

Mainly ethical issues in clinical trials involving nanomedicines revolve around such risk minimization, risk management, and risk communication. Risk minimization involves identifying factors that can be risky in human subjects and controlling them during clinical or preclinical trials. This can be done through robust literature survey, proper observation, and recording of data during the clinical trials and even following up of subjects after the study is completed. Mainly in the case of nanomedicines, the biggest failures are due to their toxicity (Sprung and Eidelman, 1997).

Thus, in vitro assays to study their basic chemical and physical properties in animal or human cell cultures and in vivo assays to study ADMAnanomedicines in rodents are of extreme importance. The NCI, mainly for cancer treatment and diagnosis, conducts in vitro and in vivo experiments on nanomaterials. Additionally many other international agencies like NIEHS, the Environmental Protection Agency (EPA), the National Science Foundation (NSF), and the National Institute for Occupational Safety and Health (NIOSH) also determine risks of exposure to these nanomedicines (Moher et al., 1996).

Researchers have identified the basic factors one needs to consider for minimizing risks of nanomedicines. Firstly, the risk of nanomedicines varies as per the route of administration such as oral, pulmonary, parenteral, etc. Secondly, the diversity of nanomaterials
makes it difficult to give a generalized statement regarding its safety and toxicity; each nanomedicine needs to be studied individually. Thirdly, the risk of manufactured nanomaterial is different from the risk of naturally occurring nanomaterial. Fourthly, the size and shape of nanomedicines change as per the microenvironment, or when it enters the organism, thus changing the risk. In addition, some heavy metals like lead may accumulate in the body and exert toxic effects. Thus by judiciously controlling all these factors, one can minimize the risk associated with nanomaterials (Sharma et al., 2015).

Risk management involves ensuring a good risk to benefit ratio. Benefits achieved from the nanomedicines should outweigh the risks to meet the ethical and legal requirements. If phase 1 clinical trials are undergoing for medical device based nanomedicines for chemotherapy, then this will involve cancer patients. However, as these are just phase 1 trials, they are not receiving any benefits; still, one needs to consider that society will benefit as this proposed system will enhance delivery of nanomedicines to target cells and reduce side effects (Oberdörster, 2010).

Risk communication ensures that informed consent from the participants in the clinical study will clearly dictate the possible risks involved during their participation. Basic information needs to be given to the subjects like the goal of the study, risks, benefits, cost, procedure, confidentiality, any compensation for injury, and willingness to withdraw from the study (Pidgeon and Rogers-Hayden, 2007).

Thus mainly in clinical trials, it is the sole duty of the investigators and their teams to obtain informed consent and properly ensure that the outcomes of the investigation will be beneficial for the society over the existing treatment and strategy availed.

18.5 ETHICS IN NANOMEDICINES

Nanomedicines are gaining utmost attention in the 21st century. However, investment in research and development of nanomedicines is very high making them expensive, and their sales also do not compensate for the research cost accrued over many years. Thus developed countries like the United States are continuously trying to make newer advancements in nanomedicines to improve the existing treatment strategies.

On the other hand, in underdeveloped countries like India investment in nanomedicines is meager and also unaffordable for the poor. Thus there is a fear that the nanodevices will create a gap between the rich and poor. Nanoethics lags behind due to lack of policies related to funding and educational institutions. Thus one should promote equity and nondiscrimination of nanomedicines as one of the ethics of nanomedicines (Resnik and Tinkle, 2007b).

Another ethical problem involves the demarcation between therapy and enhancement. Red blood cells that hold a reservoir of oxygen. Heart attack patients administered with these cells can receive oxygen and thus continue breathing until they receive proper medical treatment (Miller, 2003). On the other hand, these red blood cells are also used by athletes for body enhancement and boosting their performance. How ethical is it to use such cells for enhancement? Another issue regards hybrid humans, that is, hybrids between humans and machines. Thus although
nanomedicines bring about enhancement compared with conventional medicines, still one needs to consider their proper therapeutic use before promoting such interventions (Linkov et al., 2008).

Biocompatibility and toxicity of nanomaterials should be studied during preclinical and clinical studies. As nanomedicines tend to break down in smaller particles within the body or can even form aggregates thus causing toxicity, short term and long term nanotoxicity studies should be carried out to ensure the safety and efficacy of nanomaterials. Informed consent must be obtained from the participants of the clinical study by the investigators. They should be informed regarding the risks, procedure, duration, and benefits of the study (Silva Costa et al., 2011).

It is unethical to involve those participants who have not signed the informed consent form. Nanochips can detect any abnormality in the body or cancerous cells or gene responsible for the disease but at the same time can also predict the occurrence of disease in the near future by analyzing DNA. The latter can create anxiety, panic, and increased fear of illness, causing psychological harm. Thus nanomedicines’ hyperdiagnosis and hypertheraphy should be prevented (Mody et al., 2014).

In the case of diagnostic nanomedicines, false positive results about particular gene expression in cancer lead to improper treatment. Thus it is the responsibility of the technician to ensure that results obtained by such devices are true and reflect the inherent conditions in the body. Interpretation of results obtained by these diagnostic nanodevices by a non-technical person should be avoided (Choudhury et al., 2017; Watson, 2007).

18.6 CONCLUSION

The chapter revealed the differences among the leading regulatory bodies of the world in medicine. We can conclude that some areas are more advanced in marketing nanomedicines than others. These regional differences call for close collaboration of various regulatory bodies to share experiences and to train scientists who will be confronted with more nanomedical applications in the future. Additional challenges such as the evaluation of “nanosimilars,” borderline, and combination products will require special regulatory awareness and are already on the agenda of international working groups.

References
REFERENCES


Ehmann, F. Pis, R., 2016. The EU is ready for non-biological complex medicinal products. GABJ 5, 30–35.


BASIC FUNDAMENTALS OF DRUG DELIVERY


REFERENCES


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NON-PRINT ITEM

Abstract
The last few decades witnessed the emergence of nanotechnology in the pharmaceutical sector and the reason for the expansion and evolution of nanomedicines. Nowadays, nanoscale modalities are leading the healthcare sector from the front. However, this emerging field of science creating new challenges for the research community, industry, and regulators. The major problem in using nanomedicines is the complex characterization procedure that also varies from product to product. The characteristics of nanomedicines are required to be understood in such a way to minimize their unwanted effects for better patient compliance. This chapter emphasizes the current updates on various regulatory bodies such as US FDA, TGA, and EMA in relation to the regulatory requirement for the suitable use of nanomedicines.

Keywords: Nanomedicines; nanosimilars; regulatory requirements; regulatory bodies; approved nanomedicines; US-FDA; TGA; EMA